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TI Role of estrogen replacement therapy in memory enhancement and the prevention of neuronal loss associated with Alzheimer's disease.
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Adonis & Microfilm

AB Recent evidence supports a role for estrogens in both normal neural development and neuronal maintenance throughout life. Women spend 25-33% of their life in an estrogen-deprived state and retrospective studies have shown an inverse correlation between dose and duration of estrogen replacement therapy (ERT) and incidence of **Alzheimer**'s disease (AD), suggesting a role for estrogen in the prevention and/or treatment of neurodegenerative diseases. To explore these observations further, an animal model was developed using **ovariectomy** (OVX) and **ovariectomy** with estradiol replacement (E2) in female Sprague-Dawley rats to mimic postmenopausal changes. Using an active-avoidance paradigm and a spatial memory task, the effects of estrogen deprivation were tested on memory-related behaviors. OVX caused a decline in avoidance behavior, and estrogen replacement normalized the response. In the Morris water task of spatial memory, OVX animals showed normal spatial learning but were deficient in spatial memory, an effect that was prevented by estrogen treatment. Together these data indicate that OVX in rats results in an estrogen-reversible impairment of learning/memory behavior. Because a plethora of information has been generated that links decline in memory-related behavior to dysfunction of cholinergic neurons, the effects of estrogens on cholinergic neurons were tested. We demonstrated that OVX causes a decrease in high affinity choline uptake and choline acetyltransferase activity in the hippocampus and frontal cortex; ERT reverses this effect. Further, we showed that estrogens promote the expression of mRNA for brain- derived neurotrophic factor (BDNF) and nerve growth factor (NGF), 2 neurotrophic substances that have been shown to ameliorate the effects of age and injury on cholinergic neurons. Tissue culture models were used to evaluate whether estrogen treatment increases the survival of neurons when exposed to a variety of insults. 17-β-Estradiol (β-E2) protects cells from the neurotoxic effects of serum deprivation and hypoglycemia in human neuroblastoma cell lines. We have also observed that 17-α-estradiol (α- E2), a weak estrogen, shows neuroprotective efficacy in the SK-N-SH cell line at concentrations equivalent to β-E2. Finally, we have observed that tamoxifen, a classic estrogen antagonist, blocks only one-third of the neuroprotective effects of either α-E2 or β-E2. Collectively, these results indicate that estrogen is behaviorally active in tests of learning/memory; activates basal forebrain cholinergic neurons and

neurotrophin expression; and is neuroprotective for human neuronal cultures. We conclude that estrogen may be a useful therapy for AD and other neurodegenerative diseases.